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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/924,099	08/08/2001	Yoshihiro Nishida	NISHIDA=3A	3370

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EXAMINER	
JIANG, DONG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/924,099	NISHIDA ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/338,511.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's amendment filed on 31 August 2004 is acknowledged and entered. Following the amendment, claims 47-51 are amended.

Currently, claims 47-54 are pending and under consideration.

Withdrawal of Objections and Rejections:

The objection of claim 51 is withdrawn in view of applicant's amendment.

New Matter Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have not pointed out, nor can the Examiner locate in the specification, the concept/definition for the "variants of the amino acid sequences of the constant regions" in the newly amended claims 47-50, respectively.

Objections and Rejections under 35 U.S.C. 112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47-54 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 47 remains indefinite because it is unclear what it is meant by "*variants* of the amino acid sequences of the constant regions of ..." in lines 9-10. There is no limitation of any

kind in the claim defining such variants, and the specification does not define such either. Further, as the term "variants" is plural, it is unclear how many variants said peptide comprises. The metes and bounds of the claim cannot be determined.

Claims 48-50 are similarly indefinite.

The remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 47-54 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Taniguchi et al. (J Immunol. Methods, 1997, 206: 107-113), in view of Kohno et al. (Clin. Immunol. Immunopath., January 1998, 86(1): 11-15), and Riechmann et al. (Nature, 1988, 332:323-327), for the reasons of record set forth in the previous Office Action, paper No. 12, mailed on 27 August 2003, at pages 3-4.

Applicants argument filed on 31 August 2004 has been fully considered, but is not deemed persuasive for reasons below.

At pages 7-8 of the response, the applicant argues that Taniguchi never teaches that the mAb is effective to treat RA, and does not disclose the peptide of the presently claimed invention; that Kohno never confirms if IL-18 antibody is effective to treat the diseases such as

diabetes and RA, nor discloses the peptide of the presently claimed invention, and suggest nothing about whether the peptide of the present invention is effective to treat RA; and that Riechmann does not disclose a general technique for making humanized antibody, but discloses an "antibody against CAMPATH-1 antigen" only. This argument is not persuasive for the reasons of record set forth in the last Office Action mailed on 07 April 2004, at page 4, as applicant's argument is against the references *individually*, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, even though none of the references teaches an artificially produced peptide capable of neutralizing IL-18, and its use in the treatment, suggestion or motivation to do so can be found based on *combination* of references, which teach a mouse anit-human IL-18 monoclonal antibody capable of neutralizing IL-18 (by Taniguchi), a pathological role of IL-18 in diseases such as RA and methods of administering anti-IL-18 antibodies for treating a pathological condition (by Kohno), and a method of making a humanized antibody minimizing the anti-globulin response during therapy (by Riechmann). Therefore, it is logical and obvious to a skilled artisan to antagonize the action of IL-18 in treating RA by using an artificially produced peptide capable of neutralizing IL-18, such as a humanized antibody. A person of ordinary skill in the art would have been motivated to do so for disease treatment in humans, and for minimizing the potential side effect of the non-human antibody based on the teachings of the three references.

At pages 8-9 of the response, the applicant argues that even if humanized antibodies of the anti-IL-18 antibodies disclosed in Taniguchi or Kohno are obtained in accordance with the teachings of Riechmann, it is unclear whether said antibodies are effective to treat RA until the experiment is carried out, that the examiner has used hindsight to reconstruct applicants claimed

invention, which is not proper according to case law, and that applicants believe that certainty is required for an invention relating to a method for treating a living body. This argument is not persuasive because "certainty" of success is not a standard to apply in obviousness rejections, rather, according to MPEP 2141, *reasonable expectation* of success is the standard with which obviousness is determined. Reasonable expectation of success based on the combined teachings of the cited references, as addressed above, is not hindsight reconstruction.

At pages 9-10 of the response, the applicant argues that Riechmann discloses that the humanized rat CAMPATH-1 antibody shows drastically decreased binding activity to CAMPATH-1, indicating that making a humanized antibody may result in losing inherent functions of the antibody so that the humanized antibody is not capable of being used to neutralize an antigen, that it would not have been obvious to those of skill in the art whether making a humanized antibody is indeed advantageous, and that none of the cited references either alone or in combination provides reliable information about the effectiveness of the claimed humanized antibody in treating RA. This argument is not persuasive because Riechmann merely reported one incidence during the process of making the humanized antibody, where the antibody with the reshaped heavy chain domain bound poorly to the antigen (page 326, the first paragraph of the left column, as pointed out by applicants). However, in a subsequent experiment, the affinity of the reshaped antibody was restored by a single mutation (page 326, the second paragraph of the left column), and Riechmann concludes that the reshaped human antibody is as effective as the rat antibody in complement and is more effective in cell-medicated lysis of human lymphocytes (the abstract). With respect to the argument of effectiveness or lack thereof, once again, "certainty" of success is not a standard to apply in obviousness rejections.

Conclusion:

No claim is allowed.

Advisory Information:

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Dong Jiang, Ph.D.
Patent Examiner
AU1646
11/22/04

LORRAINE SPECTOR
PRIMARY EXAMINER